REMARKS UNDER 37 CFR § 1.111

Formal Matters

Claims 2-26 are pending after entry of the amendments set forth herein.

Claims 16-24 are pending, but are withdrawn from consideration.

Please replace claims 2-15, 25 and 26 with the clean version provided above.

Attached hereto is a marked-up version of the changes made to the claims by the current amendment. The attached is captioned "**VERSION WITH MARKINGS TO SHOW CHANGES MADE.**"

Status of application

The cover page of the Office Action indicates that claims 1-9, 11, 13, 14, 25, and 26 are rejected. However, no reasons are given in the Office Action for why claims 6-8 are not patentable. Accordingly, applicants understand that claims 6-8, 10, 12, and 15 are *ALLOWED*.

By way of this amendment, claim 1 is canceled without prejudice, and claims 25 and 6 are amended. Claims 25 and 6 are amended to incorporate the limitations of claim 1 as originally filed. Additional support for these amendments is found throughout the specification at, for example, page 8, lines 2-3 and 21-22.

Claims 2, 8-14, 16, 19, and 20 are amended to correct dependencies in view of the cancellation of claim 1.

No new matter has been added.

Applicants request reconsideration of claims 25, 2-5, 26, 9, 11, 13, and 14 in view of these amendments and the remarks below.

Upon allowance of this application, please renumber the claims in the order provided above such that current claim 25 becomes claim 1, and current claim 26 follows present claim 6.

Specification

The Office Action indicates that there are numerous typographical errors throughout the specification. Applicants undertake to review the specification and correct any errors upon indication

that the application is otherwise in condition for allowance. Applicants would appreciate clarification as to the location of any specific typographical errors known to the Examiner.

Obviousness-Type Double Patenting

Claims 1, 2, 5, 9, 11, 13, 14, 25, and 26 stand rejected for obviousness-type double patenting with respect to U.S. Patent 6,203,787. The Office Action indicates that a terminal disclaimer would cure both of these rejections.

Without commenting on the merits of the rejections, applicants point out that in any event, it is unnecessary to file a terminal disclaimer with respect to this patent. The term of any patent issuing from the present application will expire on the same day as U.S Patent 6,203,787, pursuant to 35 USC § 154(a)(2), since this application claims the priority basis of the '787 patent. Nevertheless, to facilitate prosecution of this application, applicants will file a terminal disclaimer over the '787 patent upon indication that this application is otherwise in condition for allowance.

Rejection under 35 USC § 103(a) - U.S. Pat. No. 6,203,787

Claims 1, 2, 5, 9, 11, 13, 14, 25 and 26 stand rejected under §103(a) as being obvious over U.S. Pat. No. 6,203,787 ('787). This rejection is respectfully traversed.

The present application was filed on or after November 29, 1999. As noted in the Office Action, this rejection can be overcome by showing that the subject matter of the '787 patent and the claimed invention were, at the time the invention was made, owned by the same person or subject to an obligation to assignment to the same person. MPEP §§706.02(l)(1) and (2). Specifically, 35 U.S.C. §103(c) states:

> (c) Subject matter developed by another person, which qualifies as prior art only under subsection **(e)**, (f), **and** (g) of section 102 of this title, shall not preclude patentability under this section where the subject matter and the claimed invention were, at the time the invention was made, owned by the same person or subject to an obligation of assignment to he same person. (emphasis added)

Without conceding as to the grounds of this rejection, applicants provide here evidence that the subject matter of the '787 patent and the claimed invention were, at the time the invention was made, owned by The Regents of the University of California or subject to an obligation to assignment to The Regents of the University of California.

The '787 patent was owned by The Regents of the University of California at the time the

invention was made, as evidenced by an assignment by the inventors James Thompson and Gale Granger to The Regents of the University of California, recorded on April 5, 1999 (Reel/Frames 9871/547-549) (copy enclosed).

The present application is also under an obligation to be assigned to The Regents of the University of California, since each of the inventors, James Thompson, John C. Hiserodt and Gale Granger are obligated to assign their interests to The Regents of the University of California. Applicants will provide evidence of such obligation to assign or a copy a recorded assignment with the next communication.

Therefore, since both the '787 patent and the instant application were, at the time the invention was made, subject to an obligation to assignment and owned by the Regents of the University of California, the '787 patent is not available as prior art against the claimed invention of the present application.

Rejections under 35 USC § 102(b)

Claims 1, 2-5, 26, and 9 stand rejected under 35 USC § 102(b) as being anticipated by Kohler et al., Cancer Immunol. Immunother. 26:74, 1988.

Claims 1, 2, 8, and 13 stand rejected under 35 USC § 102(b) as being anticipated by Philips et al. (J. Exp. Med. 159:993, 1984).

By way of this amendment, applicants have cancelled claim 1, and incorporated the limitations of claim 1 into claim 26 and claim 6. Claim 25 has been amended to indicate that the pharmaceutical composition of claim 25 is formulated for administration into a solid tumor or the bed of a solid tumor. Claim 6 as amended contains no new limitations, and accordingly is entitled to protection for the whole range of equivalents to which it was previously entitled.

Applicants respectfully submit that the claims as amended are patentable, and are not anticipated or fairly suggested by these references either alone or in combination.

Kohler et al.

The Kohler reference refers to a trial in which cancer patients having a cancer of circulating white cells (lymphoma or melanoma) were infused *intravenously* with HLA-haploidentical lymphocytes activated in culture with third-party leukocytes. The purpose apparently is to give the patient matched lymphocytes that have been activated to stimulate an immune response against the administered cells, leading to killing of the circulating host cells having the cancer.

In contrast, in the invention claimed in this application (and without intending any limitation by theory), the objective is not ultimately to stimulate an immune response against the administered cells, but to stimulate an immune response against bystander tumor antigen. The claims now require that the composition be formulated for administration into a solid tumor or tumor bed (claim 25) or in combination with tumor antigen (claim 6), so that the tumor antigen will be in sufficient proximity to the activated lymphocytes in order to play the role of bystander antigen. None of these features is taught or suggested by the Kohler reference.

Phillips et al.

The Phillips reference refers to a study of natural killer cells prepared in tissue culture. This is an academic study designed to make and characterize specialized leukocytes that can be prepared in vitro. The invention claimed in this patent application is not designed to make killer cells directly out of the patient's own cells in culture, but to administer third-party donor lymphocytes to the patient in order to activate the patient's immune system in situ.

Furthermore, there is no teaching in the Phillips reference to use the activated cells to manufacture a pharmaceutical composition, or for any other clinical purpose. In particular, the reference does not teach or suggest formulating activated lymphocytes for administration to a solid tumor, or in conjunction with tumor antigen.

Withdrawal of these rejections is respectfully requested.

Rejection under 35 USC § 103(a) - Phillips

Claim 13 stands rejected under § 103(a) as being obvious over a combination of the Kohler reference and the Phillips reference.

Applicants respectfully disagree. There is no motivation to combine the references in the manner indicated. The Kohler reference relates to administration of matched cells into the circulation of cancer patients apparently to elicit a response against the administered cells. In contrast, the Phillips reference is an *in vitro* culture experiment which are designed not to create an immunogenic composition, but a cell that can directly kill a target cell. Since the references are directed to different purposes, it would not make sense to combine them in the manner suggested in the Office Action.

Applicants note the following points of relevant law:

1) Even if a combination of references teaches every element of a claimed invention, without a motivation to combine the references, a rejection based on a prima facie case of obviousness is improper. *In re Rouffet,* 47 USPQ2d 1453 (Fed. Cir. 1998).

2) The proposed modification cannot render the prior art unsatisfactory for its intended purpose. If proposed modification would render the prior art invention being modified unsatisfactory for its intended purpose, then there is no suggestion or motivation to make the proposed modification. *In re Gordon*, USPQ 1125 (Fed. Cir. 1984).

Since there is no motivation to combine the references in the manner indicated, the rejected claim is patentable under 35 USC § 103. Applicants also submit that the combined references do not teach the claimed invention *inter alia* for the reasons indicated earlier in this response. It is unnecessary for applicants to comment further, since the lack of motivation to combine the references is sufficient to overcome this rejection.

Withdrawal of all outstanding rejections is respectfully requested.

Conclusion

Applicant submits that all of the claims are in condition for allowance, which action is requested. If the Examiner finds that a telephone conference would expedite the prosecution of this application, please telephone the undersigned at the number provided.

The Commissioner is hereby authorized to charge any underpayment of fees associated with this communication, including any necessary fees for extensions of time, or credit any overpayment to Deposit Account No. 50-0815, order number IRVN-005CIP.

Respectfully submitted,
BOZICEVIC, FIELD & FRANCIS LLP

Date: Dec 5, 2002

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VERSION WITH MARKINGS TO SHOW CHANGES MADE

Please cancel claim 1 without prejudice.

25. **(Amended)** ~~The composition of claim 1, which is~~ **A pharmaceutical composition comprising alloactivated lymphocytes in a compatible pharmaceutical excipient,** formulated for administration into ~~a tumor or tumor bed~~ **a solid tumor or the bed of a solid tumor in a human patient**, wherein administration of the composition into a tumor or tumor bed in ~~the~~ a patient elicits an immunological response by the patient against the tumor.

2. **(Amended)** The composition of claim ~~1~~ **25**, comprising lymphocytes from at least two different humans.

6. **(Amended)** ~~The composition of claim 1, further comprising a~~ **A pharmaceutical composition suitable for administration to a human, comprising alloactivated lymphocytes and a tumor associated antigen in a compatible pharmaceutical excipient, wherein administration of the composition to a patient having a tumor elicits an immunological response by the patient against the tumor**.

8. **(Amended)** The composition of claim ~~1~~ **25**, wherein the lymphocytes are alloactivated by coculturing with human cells *ex vivo* expressing HLA-DR antigens that are allogeneic to both HLA-DR antigens on the lymphocytes.

9. **(Amended)** The composition of claim ~~1~~ **25**, wherein the lymphocytes are alloactivated by coculturing with allogeneic human cells *ex vivo* for a time whereby the lymphocytes become sufficiently alloactivated to be effective in eliciting an anti-tumor immunological response when administered to a human.

10. **(Amended)** The composition of claim ~~1~~ **25**, wherein the lymphocytes are alloactivated by coculturing with allogeneic human cells *ex vivo* for a time whereby the lymphocytes become sufficiently alloactivated to be effective in extending life expectancy or causing progressive reduction in tumor mass when administered to a human having a tumor.

11. **(Amended)** The composition of claim ~~1~~ **25**, wherein the lymphocytes are alloactivated by coculturing with allogeneic human cells *ex vivo* until about the time when secretion of IFN-γ by the alloactivated lymphocytes is highest.

12. **(Amended)** The composition of claim ~~1~~ **25**, wherein the lymphocytes are alloactivated by coculturing with allogeneic human cells *ex vivo* until about the time when secretion of IL-2 by the alloactivated lymphocytes is highest.

13. **(Amended)** The composition of claim ~~1~~ **25**, wherein the lymphocytes are alloactivated by coculturing with allogeneic human cells *ex vivo* for between about 12 hours and 5 days.

14. **(Amended)** The composition of claim ~~1~~ **25**, wherein the lymphocytes are alloactivated by coculturing with allogeneic human cells *ex vivo* for between about 24 and 72 hours.

16. **(Amended)** A device for treatment of a tumor in a human patient, containing the composition of claim ~~1~~ **25**.

19. **(Amended)** A method for treating cancer in a human patient, comprising administering to the patient the pharmaceutical composition of claim ~~1~~ **25**.

20. **(Amended)** A method for eliciting an anti-tumor immunological response in a human patient, comprising administering to the patient the pharmaceutical composition of claim ~~1~~ **25**.